REMARKS

Receipt is acknowledged of the Office Action mailed August 19, 2003. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and these remarks.

In the specification, paragraph numbers 128 and 146 have been amended.

Claims 1-6 and 24-27 are requested to be cancelled.

After amending the claims as set forth above, claims 7-20 are now pending in this application. Claims 4 and 5 stand rejected under 35 USC § 112, ¶ 2 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In addition, claims 1-6, 24 and 26-27 stand rejected under 35 USC § 112, ¶ 1 as allegedly failing to comply with the enablement requirement. Claims 7-20 stand rejected under 35 USC § 112, ¶ 1 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Claims 1-5 and 24-27 also stand rejected under 35 USC § 102(b) as allegedly being unpatentable over Roberts *et al.* (A1). Finally, claim 6 stands rejected under 35 USC § 103(a) as allegedly being unpatentable over Roberts *et al.* (A1) in view of either Shittagar (A) or Kinstler *et al.* (B).

Objections

The Examiner objects to the disclosure for three reasons. First, the Examiner objects to Figure 8 because the figure is a black box. Applicants herein resubmit Figure 8 with a replacement graph depicting the relationship between activity and pH.

Second, the Examiner objects to Table 1 because the meaning of the table is unclear. The Examiner indicates that he understands the term "coordinates" to mean the residue positions of the identified sequence in SEQ ID NOS: 13-31. The Examiner further indicates that the table shows the coordinates as, for example, 838-867 for SEQ ID NO: 13, when SEQ ID NO: 13 only

has 30 residues. Applicants respectfully submit that the term "coordinates" indicates the position relative to ATG start codon on SEQ ID NOS: 7 or 12. Applicants have amended paragraph number 128 in order to make this meaning clear.

Finally, the Examiner objects to paragraph number 146 because, although the paragraph states that the application depicts a graph below, no graph exists below the paragraph. Applicants respectfully submit that their amendment to paragraph number 146, which removes the objectionable sentence cures this defect. Applicants respectfully request that the Examiner withdraw these objections.

35 USC § 112, ¶ 2

Claims 4 and 5 stand rejected under 35 USC § 112, ¶ 2 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Without acquiescing in the rejection and without intending to abandon claimed subject matter but to expedite allowance, claims 4 and 5 have been cancelled. Thus, applicants respectfully submit that this rejection is moot.

35 USC § 112, ¶ 1: Enablement

In addition, claims 1-6, 24 and 26-27 stand rejected under 35 USC § 112, ¶ 1 as allegedly failing to comply with the enablement requirement. Without acquiescing in the rejection and without intending to abandon claimed subject matter but to expedite allowance, claims 1-6, 24 and 26-27 have been cancelled. Thus, applicants respectfully submit that this rejection is moot.

35 USC § 112, ¶ 1: Written Description and Enablement

Claims 7-20 stand rejected under 35 USC § 112, ¶ 1 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention and in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Without acquiescing in the rejection and without intending to abandon claimed subject matter but to expedite allowance, claims 8 and 12 have been amended. Claims 8 and 12 have been amended to recite an isolated polypeptide having about 40 IU/mg protein of histidine ammonia lyase activity. This amendment has been made to support applicants assertion in the last response that this amendment was being made.

Applicants, however, disagree with the Examiner's assertions that the specification does not disclose histidine ammonia lyases from organisms other than *Corynebacteriaceae* and histidine analogs other than L-histidinol. The specification indicates that histidine ammonia lyases have been isolated from several bacterial, animal, mammalian and plant sources. *See* page 3, paragraph 8. *See also* Shibatani *et al.*, *Eur. J. Biochem.* 55: 263-269 (1975). Specifically, the specification discloses that histidine ammonia lyases can also be isolated from bacteria such as *Achromobacter liquidum* and *Streptomyces griseus*. *See* page 5, paragraph 8. In addition, the specification demonstrates the antiviral activity of histidine antagonism through the use of histidine analogs, histidase and histidinol. *See* Examples 1 and 9. Thus, applicants respectfully submit that this disclosure supports and enables the broad scope of claim 7 without the added limitations recited in claim 8.

Additionally, the Examiner does not allege that the specification fails to enable a method of treatment, comprising administering to a patient suffering from a viral infection a therapeutic amount of a polypeptide having about 40 IU/mg protein of histidine ammonia lyase activity, where the histidine ammonia lyase activity is not decreased in the presence of L-histidinol or a therapeutic salt thereof and that the polypeptide corresponds in sequence to histidine ammonia lyase of *Corynebacteriaceae* or to a fragment thereof which includes the active site as claimed. Thus, applicants respectfully submit that claim 8 contains allowable subject matter.

With respect to the conservative substitutions claimed in claims 8 and 12, applicants submit that these are also enabled by the specification. The specification discloses sequence variations that are contemplated by the invention. See page 15, paragraph 53. For example, according to SEQ ID NO: 6, the amino acids represented by "X" can be an amino acid that is

present in the corresponding position of any other histidine ammonia lyase. Amino acid positions delineated by "X" represent regions where the amino acid can vary without departing from the invention. For instance, figure 14 denotes Alanine at position 14 of the HAL isolated from *Corynebacteriaceae.* In histidine ammonia lyases isolated from those species depicted in figure 14, the amino acid at the position corresponding to position 14 in *Corynebacteriaceae* are: threonine, alanine, valine, leucine, asparagine, aspartic acid, and proline, as shown in figure 14. One of skill in the art would understand how to make and use these variants in accordance with the claimed method. Thus, the claimed variants are enabled by the specification.

In addition, with respect to claims 16-20, the specification discloses that the products of the enzymatic action of histidine ammonia lyase are trans-urocanic acid (t-UA) and ammonia. The specification discloses how the polypeptide generates trans-urocanic acid (t-UA) *in vivo* and can be used to generate circulating t-UA. See page 26, paragraph number 82. In addition, the specification, discloses how subjecting a patient to an irradiating agent causes the photoisomerization of t-UA to its cis isomer (c-UA), and subsequently the cis isomer comprises the immunosuppressive property.

The specification also notes that it is well-known by those of skill in the art that irradiation at approximately 310 nm causes the photoisomerization of t-UA to its cis isomer (c-UA). This is disclosed by Hanson *et al.*, *Proc. Natl. Acad. Sci. USA* 95: 10576-10578 (1998). It is also known by those of skill in the art that cis-urocanic acid plays the role of one of the UVB-induced immunosuppressive mediators (Kripke, *Cancer Res.* 54: 6102-6105 (1994); and Norval *et al.*, *Photochem. Photobiol.* 62: 209-217 (1995)). This immunosuppressive property of urocanic acid can be used, for example, to treat immune system disorders and to prevent rejection of transplanted organs.

In a preferred embodiment, the specification discloses that PEGylated HAL is used. See page 26, paragraph number 82. PEGylated HAL has a long circulatory half-life in mice (over 48 hours). Thus, an effective dose (1 μg to 1 g per kg body weight) of a histidine ammonia lyase can be used to generate circulating urocanic acid for prolonged periods of time. This overcomes

a problem with administering urocanic acid which, being a small molecule, is rapidly cleared from circulation. Following administration of HAL, a cis-isomerizing agent such as UVB irradiation is used to cause local immunosuppression (for conditions such as psoriasis), or systemic immunosuppression, the process of which subjects the patient to whole body irradiation. In one example, whole body irradiation can be employed according to the invention, to combat organ rejection following transplantation. In another embodiment, selective immunosuppression can be achieved by targeting the UVB irradiation. For example, psoriasis could be treated by an injection of a histidine ammonia lyase followed by selective irradiation of the affected areas. Selective UVB irradiation, following the injection of a histidine ammonia lyase into a patient, can also be used to treat conditions like arthritis. Applicants believe that, based on the disclosure in the specification, a skilled artisan would understand how to make and use the claimed invention and would further understand that the inventors, at the time the application was filed, had possession of the claimed invention.

Reconsideration and withdrawal of the rejection under the first paragraph of Section 112 is respectfully requested.

35 USC § 102(b)

Claims 1-5 and 24-27 also stand rejected under 35 USC § 102(b) as allegedly being unpatentable over Roberts *et al.* (A1). Without acquiescing in the rejection and without intending to abandon claimed subject matter but to expedite allowance, claims 1-5 and 24-27 have been cancelled. Thus, applicants respectfully submit that this rejection is moot.

35 USC § 103(a)

Finally, claim 6 stands rejected under 35 USC § 103(a) as allegedly being unpatentable over Roberts *et al.* (A1) in view of either Shittagar (A) or Kinstler *et al.* (B). Without acquiescing in the rejection and without intending to abandon claimed subject matter but to expedite allowance, claim 6 has been cancelled. Thus, applicants respectfully submit that this rejection is moot.

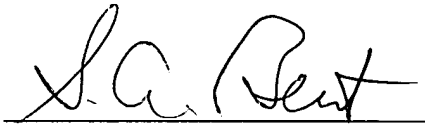
Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 20 January 2004

By 

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